



**INTERNATIONAL PROGRAMME ON CHEMICAL SAFETY**

**IPCS Report**

**IPCS Harmonization Project  
Cancer Framework Workshop**

**21-23 April 2005, Bradford, United Kingdom**

**INTERNATIONAL PROGRAMME ON CHEMICAL SAFETY (IPCS)  
HARMONIZATION PROJECT**

**Report of the Cancer Framework Workshop**

**21-23 April 2005, Bradford, United Kingdom<sup>1</sup>**

**ITEM 1: WELCOME AND OPENING OF WORKSHOP**

1. The Harmonization Project International Cancer Framework Workshop was convened on 21-23 April 2005, at the University of Bradford, Bradford, United Kingdom.
2. The workshop was opened by the Vice-Chancellor of the University of Bradford, Prof. Chris Taylor. Prof Taylor welcomed participants to Bradford and its University. He mentioned that the IPCS effort on cancer risk assessment methods had commenced with a series of meetings in the UK, and that it was a pleasure to host this international workshop which will mark an important milestone in this activity. In closing, he wished participants well in their task over the next few days.
3. On behalf of IPCS, Ms. Carolyn Vickers welcomed participants (a list of invited participants appears at Annex 1). She explained the main purpose of the workshop was to develop and refine an IPCS unified cancer framework based on the *IPCS Conceptual Framework for Evaluating a Mode of Action for Chemical Carcinogenesis* and the International Life Sciences Institute Risk Science Institute (ILSI/RSI)-developed Human Relevance Framework, taking into account the views of the IPCS Cancer Working Group convened in Arlington, Virginia, USA, in March 2004. She thanked the IPCS Cancer Working Group for their contribution to the preparations for this meeting, Dr. Douglas McGregor for developing the case studies (in consultation with the Group), and Dr. Jerry Rice for the preparation of two issues papers (which were initially considered at the Arlington meeting). She thanked Prof. Diana Anderson and her staff for their excellent local preparations for the meeting.
4. After a round of introductions, Ms. Vickers advised participants that Dr. Bill Farland, the Cancer Working Group Chair, was unable to participate in the workshop and sent his sincere apologies and best wishes for the workshop. In addition, she referred to the "Chairman's Draft Integrated Framework" Dr. Farland

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had prepared and which had been distributed to participants. Hence, the workshop proceeded to consider a Chair for its session, and elected Prof. Alan Boobis. After assuming the Chair, Prof. Boobis turned to selection of a Rapporteur, with the workshop agreeing on Dr. Jerry Rice.

5. As local host, Prof. Diana Anderson, Bradford University, also extended a warm welcome to participants, and provided information on the workshop logistics.

#### **ITEM 2: ARRANGEMENTS FOR THE WORKSHOP REPORT**

6. The Chair outlined the arrangements for the workshop report and other publications. Using the Chairman's Draft Integrated Framework as a foundation, the workshop should agree on any additional text and other amendments to be made. In accordance with Harmonization Project procedures the full workshop report will be circulated to participants for comment after the meeting and finalized by the Chair. The IPCS publication of the framework will be posted on the internet for public comment, and subsequently finalized by a (small) group including the workshop Chair and the Working Group Chair. In addition, the final framework should be submitted for publication in the peer reviewed literature. The workshop noted the possible benefits of also publishing (some of) the case studies and agreed to come back to this point later in the workshop, at which time publication of the issues papers should also be discussed.

#### **ITEM 3: ADOPTION OF THE AGENDA**

7. The agenda was adopted as proposed (refer to Annex 2).

#### **ITEM 4: INTRODUCTION TO THE WORK TO DEVELOP AN IPCS CANCER FRAMEWORK**

8. Ms. Vickers commenced her presentation on the history of the IPCS activity by thanking Ms. Cindy Sonich-Mullin who led the Secretariat work on the original IPCS Mode of Action framework and had provided much of the presentation material. She explained that the current workshop was the culmination of a concerted effort over many years by experts engaged in both the IPCS and ILSI activities. She explained the development of the original IPCS Mode of Action framework.
9. Dr. Sam Cohen presented the next phase of activity, lead by ILSI/RSI, which focussed on development of a human relevance framework. Dr. Cohen highlighted that the ILSI framework performed two very useful functions, first, the framework forces identification of the key events, and second, data gaps become quickly apparent. He indicated some areas for further discussion and development by the workshop, including DNA-reactive substances and the issue of exposure and its separation from the final ILSI question about quantitative differences.
10. Ms. Bette Meek then summarized the views of the Arlington IPCS meeting of the IPCS Cancer Working Group on the ILSI framework, and how these might be

further considered and addressed in the Chairman's Draft. This included the wording of the questions in the ILSI framework. She further proposed that the workshop consider explicitly including "key events" in the definition of "mode of action".

11. Dr. Julian Preston was then invited to inform the workshop about his forthcoming publication (co-authored with Dr. Gary Williams) on the use of the ILSI framework for DNA-reactive carcinogens. Preston and Williams had concluded that the ILSI framework was a viable approach for the use of mechanistic data for these types of substances for predicting human carcinogenicity. They proposed 10 key events for tumour development for DNA-reactive MOAs. In the following discussion, it was observed that some of these events may be too generally described to be "key events" as previously defined by IPCS, however they would be useful to bear in mind in the evaluation process.

#### **ITEM 5: PREPARATION OF THE IPCS CANCER FRAMEWORK**

12. The Chairman explained the charge to the break-out groups which would each use two of the six case studies to explore the ILSI framework, the issues raised by the Arlington workshop, and those raised in earlier discussions at the workshop. The groups were asked to bring back to Plenary their views to inform development of the IPCS framework. Over a series of break-out group and Plenary sessions, proposals were discussed and the views of the workshop captured in a revised version of the Chairman's Draft, the "Draft IPCS Framework Text" which appears at Annex 3. Additional material covered a range of subjects including: the use of frameworks in risk assessment; definition of MOA including key events; how a MOA gains "acceptance"; application to DNA-reactive carcinogens; clarification on the issues of exposure, dynamics and kinetics; consideration of sensitive sub-populations; considerations in the statement of confidence and the explanatory text under each of the questions/steps of the framework.
13. The break-out group case study work was completed in good time, with Plenary discussion indicating a high degree of consensus about the value of the framework, and the purpose and function of each of the three questions. However the workshop struggled with how to capture this general understanding in the few words of the framework diagram questions so that it would be clear to others, including when translated into languages other than English. It was stressed that the framework diagram and its questions should not be read and employed in isolation of the explanatory text that accompanies it. However, the value of the diagram was recognized, in particular in conveying the framework to others, in presentations, in training tools, etc.. It was further noted that as the final form of the publication is revised, including through circulation to participants for comment and a round of public comment, there was an opportunity to further refine the diagram including the questions. The proposed title for the publication was: "IPCS Framework for analysing the relevance of a cancer Mode of Action for humans". It was recognized that at this stage, the framework had been discussed by IPCS in the context of cancer risk assessment, and that the title could be amended in future should the framework be extended to other end-points (see Item 7.2).

14. The conclusions of the workshop on the framework, which are also included in the framework text were:

- i. A unified IPCS Framework, based on the work by IPCS on a MOA framework and by ILSI/RSI on a human cancer relevance framework has been developed.
- ii. Many aspects of the original frameworks have been adopted but a number of changes have been made to improve clarity and to introduce some elements not previously considered (e.g. sensitive sub-populations), based on experience gained in their application from the time since their publication.
- iii. The utility of the framework as an analytical tool within the overall risk assessment paradigm, i.e. in hazard characterisation has been emphasized, and the role of exposure assessment in risk characterization has been clarified.
- iv. Prior to embarking on a framework analysis, there needs to be careful evaluation of the weight of evidence for a carcinogenic response in experimental animals.
- v. Attention is drawn specifically to the need to consider potentially susceptible sub-groups, for example in different life stages or those with certain disease states.
- vi. The importance of considering dose-effect and changes in effect at different parts of the dose-response curve leading to different key events for the MOA at different doses has been emphasized.
- vii. The need to separate key events from modulating factors and to consider their potential quantitative impact in the risk characterization was emphasized.
- viii. The framework is applicable to all carcinogens, whatever the MOA. Some guidance is provided on developing MOAs for compounds that are DNA-reactive.
- ix. The process whereby an MOA is accepted is described.
- x. It is recommended that a compendium of MOAs with agreed key events be established and maintained.
- xi. It is recommended that a database of cases where the framework has been utilized, particularly when early in the development of an MOA, should be compiled and maintained.
- xii. It is concluded that the framework is of value to both risk assessment and research communities in identifying data needs in establishing a MOA.

## **ITEM 6: FINALIZATION, ADOPTION AND USE OF THE DOCUMENT**

15. The process for finalization of the document having been discussed in general earlier, the workshop focussed on timeframes and whether or not the case studies and issues papers should be published. It was agreed that IPCS should strive to publish the draft framework on the internet for comment in June if possible, so that the final version could be published on the internet around September (the journal article would follow depending on journal timelines).
16. The workshop supported publication of the following cases, with the first-listed person leading the further development of the case with the others listed, and their "authors draft" being circulated to all participants for comment. These could be developed in parallel to the framework, aiming for September finalization. In addition, it was agreed that the cases should be published together, with an overview article tying them together and to avoid repetition. The Secretariat was asked to prepare a detailed proposed timeline.
  - a. Thiazopyr: Dr. Vicki Dellarco, Dr. Douglas McGregor, Prof. Alan Boobis, Prof. Sir Colin Berry.
  - b. 4-aminobiphenyl: Dr. Sam Cohen, Dr. McGregor, Ms. Bette Meek, Dr. Julian Preston, Prof. Boobis.
  - c. Formaldehyde/glutaraldehyde: Ms. Deborah Willcocks, Dr. McGregor, Dr. Vincent Cogliano, Dr. Hermann Bolt, Dr. Hans-Bernhard Richter-Reichhelm.
17. The workshop noted that the framework text should be checked to ensure appropriate citation of the two issues papers on site concordance and life-stage. Dr. Jerry Rice will lead the preparation of publication/s and identify others who may be interested in assisting in their finalization.
18. The workshop discussed adoption and use of the framework, noting that the uptake by many bodies of the original IPCS MOA framework provided a good foundation. This could be facilitated by the recommended repository of examples, development of training modules, and training workshops (including at national levels). Dr. Bill Wood explained that the US EPA plans to post case examples on their website and develop training modules, which offers potential for collaboration. Opportunities for presentation at scientific society meetings were discussed, for later follow-up.

## **ITEM 7: OTHER BUSINESS**

### **ITEM 7.1 Updating of the IPCS Qualitative Scheme for Mutagenicity**

19. The workshop discussed the proposal that IPCS update the Qualitative Scheme for Mutagenicity, published as Ashby et. al. *IPCS Harmonization of Methods for the Prediction and Quantification of Human Carcinogenic/Mutagenic Hazard, and for Indicating the Probable Mechanism of Action of Carcinogens*, Mutation Research, 352 (1996): 153-157.

20. The workshop concluded that a qualitative scheme for the evaluation of mutagenic potential is of considerable value in the application of the framework and that updating of the IPCS scheme is recommended. It was noted that ILSI/HESI has an ongoing activity on a minimum battery of tests for predicting carcinogenicity and that this should be taken into account by IPCS. This could be effected by cross-membership of expert groups and appropriate timing of the IPCS work. The output should include an article in the peer-reviewed literature.

#### **ITEM 7.2 Extension of the IPCS Framework to other toxicological end-points**

21. The workshop next considered the benefits of extension of the cancer framework to other toxicological end-points. Ms. Meek briefed participants on the ILSI/RSI activity to extend their published framework, which was about to be published.
22. The workshop was of the opinion that it should be possible to extend the framework to non-cancer endpoints and further work on this was recommended. The workshop felt that the present workshop was a useful model for how to build on the ILSI/RSI work and internationalize a framework approach for end-points beyond cancer.
23. Suggested next steps were to review the ILSI/RSI publication, consider the case studies contained therein, and whether the same cases could be employed in the IPCS activity. However, it would also be useful to consider new cases demonstrating application to additional end-points. Cross-membership of expert groups between ILSI/RSI and IPCS and appropriate timing of the IPCS activity were recommended. IPCS was requested to include in the outputs an article in the peer reviewed literature.

#### **ITEM 8: CLOSURE**

24. In closing the workshop on 23 April, the Chair thanked participants for their collective contribution to the success of the workshop and development of the IPCS cancer framework. On behalf of participants he expressed appreciation and thanks to Prof Diana Anderson and Ms. Christine Dove, for their kind hospitality in Bradford and preparation of the meeting, and to Ms. Vickers and Mrs. Sandra Kunz for their work in preparing for the workshop, including coordinating the development of the papers. Ms. Vickers then thanked Prof. Boobis for his expert chairmanship, in facilitating input of a range of different views into an agreed framework document and hence enabling the workshop to achieve its objectives.

**IPCS Harmonization Project Cancer Framework Workshop  
Invited Participants List**

Dr. Peter Abbott  
Scientific Risk Assessment and Evaluation Branch  
Food Standards Australia & New Zealand  
AUSTRALIA

Dr. Diana Anderson  
Professor, Chair, Department of Biomedical Sciences  
University of Bradford, Richmond Rd  
UNITED KINGDOM

Professor Sir Colin Berry  
UNITED KINGDOM

Professor Hermann Bolt  
Institut für Arbeitsphysiologie  
GERMANY

Professor Alan R. Boobis OBE  
Director of the Department of Health Toxicology Unit  
Imperial College London  
UNITED KINGDOM

Dr. Susy Brescia  
Health and Safety Executive  
UNITED KINGDOM

Dr. John Bucher  
NIEHS  
USA

Dr. Samuel M. Cohen  
Professor and Chair, Pathology and Microbiology  
Havlik-Wall Professor of Oncology  
University of Nebraska Medical Center  
USA

Dr. Vicki Dellarco  
Office of Pesticide Programs, US Environmental Protection Agency  
USA

\*\*Dr. William Farland  
Office of Research and Development, US Environmental Protection Agency  
USA

Dr. Jun Kanno  
Head, Division of Cellular and Molecular Toxicology  
National Institute of Health Sciences  
JAPAN

\*\*Dr. Ada Knaap  
Head, Toxicology Advisory Centre  
National Institute of Public Health and Environmental Protection  
NETHERLANDS

\*\*Dr. Lois D. Lehman-McKeeman  
Bristol-Myers Squibb  
USA

Ms. Bette Meek  
Environmental Health Center, Health Canada  
CANADA

Dr. Douglas McGregor  
Toxicity Evaluation Consultants  
UNITED KINGDOM

\*\* Dr. Edward V. Ohanian  
Director, Health and Ecological Criteria Division  
Office of Science and Technology/Office of Water  
U.S. Environmental Protection Agency  
USA

Dr. R. Julian Preston  
Director, Environmental Carcinogenesis Division  
US Environmental Protection Agency NHEERL  
USA

Dr. Hans-Bernhard Richter-Reichhelm  
BfR Head Working Group 63: Toxikologie der Chemikalien Thielallee  
GERMANY

Ms. Deborah Willcocks  
Existing Chemicals, NICNAS  
AUSTRALIA

Dr. William P. Wood  
Executive Director, Risk Assessment Forum  
Environmental Protection Agency  
USA

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\*\* Unable to attend.

Dr. Zheng Yuxin  
Deputy Director, Professor, Institute for Occupational Health and Poison Control,  
Chinese Center for Disease Control and Prevention  
Director, WHO Collaborating Centre of Occupational Health  
P.R. CHINA

### **Representatives**

Dr. Christian Laurent  
Senior Genetic Toxicologist, Scientific Expert Services (SES)  
European Food Safety Authority (EFSA)  
ITALY

Ms. Sharon Munn  
European Chemicals Bureau, Toxicology and Chemical Substances  
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\*\*Mme Laurence Musset  
Environment, Health and Safety Division, OECD  
FRANCE

\*\*Dr. Steve Olin  
Deputy Director, ILSI Risk Science Institute  
USA

### **Secretariat**

Dr. Antero Aitio  
International Programme on Chemical Safety, World Health Organization  
SWITZERLAND

Dr. Vincent Cogliano  
Chief, Unit of Carcinogen Identification and Evaluation  
International Agency for Research on Cancer  
FRANCE

Ms. Christine Dove  
Research Secretary, School of Life Sciences  
University of Bradford, Bradford  
UNITED KINGDOM

Dr. Janet Kielhorn  
Dept of Chemical Risk Assessment  
Fraunhofer Institute for Toxicology and Experimental Medicine  
GERMANY

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\*\* Unable to attend.

Mrs. Sandra Kunz  
Secretary, International Programme on Chemical Safety  
World Health Organization  
SWITZERLAND

Dr. Jerry Rice  
USA

Ms. Carolyn Vickers  
International Programme on Chemical Safety  
World Health Organization  
SWITZERLAND

**WORLD HEALTH ORGANIZATION  
INTERNATIONAL LABOUR ORGANIZATION  
UNITED NATIONS ENVIRONMENT PROGRAMME**

**IPCS/Cancer/05.01rev2  
21-23 April 2005  
Bradford**

**INTERNATIONAL PROGRAMME ON CHEMICAL SAFETY  
Project on the Harmonization of Approaches to the Assessment of Risk  
from Exposure to Chemicals**

**IPCS Cancer Framework Workshop**

**21-23 April 2005, Bradford University, Bradford, United Kingdom  
Commencing at 9.00 am on 21 April and concluding at 1pm on 23 April**

**Annotated Agenda**

**1. Welcome and Opening of Workshop.**

The meeting will be officially opened by the Vice-Chancellor of the University of Bradford, Prof. Chris Taylor. Ms. Carolyn Vickers will make opening remarks on behalf of IPCS, followed by Dr. Diana Anderson for the local hosts. Participants will elect a Chair for the workshop.

**2. Arrangements for workshop report.**

The workshop will be invited to agree on a Rapporteur for the Plenary discussion of the IPCS framework. The text of the framework will be agreed at the workshop, however there will be an opportunity for a final review of the document in writing following the workshop as part of finalization of the full workshop report (which will be prepared by the Secretariat).

**3. Adoption of the Agenda (Document IPCS/Cancer/05.01)**

The Chair will invite participants to adopt the agenda, amended as necessary.

**4. Introduction to the work to develop an IPCS Framework  
(Oral presentations)**

A brief historical introduction to this IPCS activity will be presented, followed by an overview of the ILSI work on a human relevance framework, and presentation of the proposed IPCS unified framework which is the subject of this workshop.

**5. Preparation of the IPCS Cancer Framework  
(Document IPCS/Cancer/05.02(Case studies))  
(Document IPCS/Cancer/05.03 (Charge to break-out groups))**

The workshop will use case-studies to test and refine the IPCS Framework, through a process of breakout groups and plenary discussion. The charge to the breakout groups will be explained.

The workshop is expected to break into groups around the middle of Day 1. Before the close of Day 1, plenary will be asked to resume for any clarification needed by the groups following their first discussion. Subsequent plenary sessions will be as agreed by the workshop.

**6. Finalization, Adoption and Use of the Document**

The workshop will be asked to propose ways to facilitate adoption and use of the document by national and international risk assessment bodies.

**7. Other Business**

**7.1 Updating of the IPCS Qualitative Scheme for Mutagenicity.  
(Document IPCS/Cancer/05.05)**

The workshop will be invited to discuss and advise on aspects of this work, proposed for 2006.

**7.2 Extension of the IPCS Framework to other toxicological end-points.  
(Document IPCS/Cancer/05.04)**

The workshop will be invited to discuss and advise on aspects of this work, proposed for later in 2005.

**8. Closure.**

The workshop is scheduled to close at 1pm on Saturday 23 April.

**Workshop Documents (Available on the e-community site)**

The workshop documents are indicated in the above agenda (in parentheses).

**Background Documents (Available on the e-community site)**

- Original IPCS Mode of Action Framework.

- Critical Reviews in Toxicology publication of ILSI work on a Human Relevance Framework (HRF). *Refer to Figure 2 at page 601 for the general HRF schematic proposed by the authors.*
- Report of the March 2004 Meeting of the IPCS Cancer Working Group. *This meeting commented on the HRF published in Critical Reviews in Toxicology (refer to paragraph 34 in particular) and on the issue of an HRF in general.*
- IPCS Harmonization of Methods for the Prediction and Quantification of Human Carcinogenic/Mutagenic Hazard, and for Indicating the Probable Mechanism of Action of Carcinogens, Mutation Research, 352 (1996): 153-157. i.e. the IPCS "Qualitative Scheme for Mutagenicity". *This document has been distributed in hard copy and is background for Agenda Item 7.2.*
- Issue Paper: Human Relevance of Animal Neoplasms: Site Concordance between Humans and Experimental Animals for Cancers Caused by Exposures to Chemical Carcinogens. *An earlier version of this paper was considered by the March 2004 Cancer Working Group meeting, in particular refer to paragraphs 36-39. As a result of comments received from the Working Group the paper was revised, and is provided for this workshop as background material.*
- Issue Paper: Human Relevance of Animal Neoplasms: Significance of Life Stage at time of Exposure to Environmental Carcinogens. *An earlier version of this paper was considered by the March 2004 Cancer Working Group meeting, in particular refer to paragraphs 36-39. As a result of comments received from the Working Group the paper was revised, and is provided for this workshop as background material.*

**IPCS HARMONIZATION PROJECT DRAFT FOR PEER REVIEW**  
**Draft prepared by IPCS Workshop, April 2005, Bradford, United Kingdom**

**IPCS FRAMEWORK FOR ANALYSING THE RELEVANCE OF A CANCER  
MODE OF ACTION FOR HUMANS**

**INTRODUCTION**

The process of cancer risk assessment has evolved over the last three decades. Fundamental to this evolution has been our increasing understanding of the biology of cancer and key events that distinguish the cancer process. Through the mid-1980s, national and international assessments of human cancer hazard and risk depended primarily on lifetime bioassays of potentially carcinogenic agents in laboratory animals. Few agents had sufficient human evidence upon which to base cancer assessments. Inherent in these animal-based assessments were the assumptions that the observation of tumours in animals was relevant to the risk of cancer in humans, and that responses observed at high doses in animals could be extrapolated meaningfully, through mathematical models, to doses of regulatory relevance for humans. These assumptions, while valid for many chemicals, were based primarily on correlative analysis. It has become increasingly apparent that an appreciable number of chemicals cause cancer in animals by a process that does not involve direct interaction with DNA. These non-genotoxic carcinogens often act indirectly, for example by causing persistent cellular damage leading to regenerative hyperplasia. As progress has been made in the last twenty years in our understanding of the mode of action (MOA) of carcinogenesis in both animals and in humans, risk assessment has benefited from the use of more data on the pharmacokinetics and pharmacodynamics of agents to determine the appropriateness of such assumptions and to characterize the biological basis underlying the use of such assumptions. The biological processes involved in some cancer MOAs are such that they are not relevant to humans, for example when a critical target such as alpha<sub>2</sub>-globulin, present in male rats, is absent in humans.

The postulated MOA is a biologically plausible hypothesis/basis for the sequence of events leading to an observed effect supported by robust experimental observations and mechanistic data. It identifies “key” cellular and biochemical events – i.e., those that are both measurable and critical to the observed effect as hypothesized in the postulated mode of action. Assessment of the weight of evidence for a hypothesized mode of action in animals and its relevance to humans is based on consideration of factors such as consistency and dose response for key events. Mode of action contrasts with mechanism of action, which generally implies a detailed description and sufficient understanding of the molecular basis for an effect so as to establish causation in molecular terms.

The IPCS Framework presented in this document is an analytical tool, to provide a means of evaluating systematically the data available on a specific carcinogenic

response to a chemical in a transparent manner. Whilst it is envisaged that the framework will be of value to risk assessors, both within and outside of regulatory agencies, it will also be a valuable tool to the research community. Amongst reasons for using the framework are:

- To provide a harmonized generic approach to the analysis of data.
- To ensure transparency of the consideration of use of available data and reasons for the conclusions drawn.
- To provide guidance in the presentation of data.
- To identify data deficiencies and needs.
- To inform the quantitative assessment of carcinogenic risk to humans.
- To explore “what-if” scenarios, such as the impact of an equivocal event (e.g. weak genotoxicity) or whether a questionable tumour response would have any human relevance even if it were real.

Amongst the strengths of the framework are its flexibility, general applicability to carcinogens acting by any mechanism and the ability to explore the impact of each key event on the carcinogenic response. This includes determination of the nature of the dose-response curve, the identification and location of thresholds for individual key events and their consequences for the overall tumour response curve. In addition, by considering the kinetic and dynamic factors involved in each key event, it may be possible to reach conclusions regarding the relevance or not of the carcinogenic response to specific sub-populations, for example in early life, in those with particular diseases or in those with specific polymorphisms. Alternatively, the framework can provide quantitative information on the differences between such groups. Application of the framework can also more generally inform in risk characterization of the chemical, even when it is concluded that the carcinogenic response per se is not relevant to humans.

As stated at the outset, MOA analysis and its human relevance counterpart are aspects of the hazard identification and characterization phases of risk assessment (NAS, 1983; Meek et al, 2003 (Appendix). Consistent with this paradigm, the human relevance case studies referred to in this report contribute to, but do not complete, a risk assessment for the chemicals under study. This is because a complete risk characterization requires analysis of human exposure in the “real world” of daily and lifetime activities, whereas hazard identification and characterization consider effects, only. This critical distinction is often overlooked or ignored.

Hazard characterization – and related MOA analysis – focuses on dose-response relationships established in laboratory or epidemiological studies that identify toxic effects. Risk characterization seeks to describe the relationship between these effects and the dose(s) to which humans are exposed in order to understand and estimate the nature and likelihood of effects in humans who are generally exposed at lower dose levels.

Estimating these generally lower human exposure levels is the task of the exposure analysis component of the risk assessment process. This usually involves extensive analysis of data collected from environmental media, and plant and animal

tissues, as well as that derived from pharmacokinetic models. This process depends also on real world analysis of human activity patterns and life style factors that may bring about exposure. Ideally, based on this information, a range of exposure scenarios is developed for different groups (men, women, children, infants, special groups, based for example on ethnicity or occupation) for use in identifying populations of concern.

## **THE ROLE OF THE INTERNATIONAL PROGRAMME ON CHEMICAL SAFETY IN DEVELOPING THE FRAMEWORK FOR ANALYSING THE RELEVANCE OF A CANCER MODE OF ACTION FOR HUMANS**

The International Programme on Chemical Safety (IPCS) has been leading an effort to harmonize approaches to cancer risk assessment as part of its larger project on the *Harmonization of Approaches to the Assessment of Risk from Exposure to Chemicals*. As described in Sonich-Mullin et al. (2001), a major impediment to harmonization identified in the consideration of weight-of-evidence was the evaluation of MOA in animals. Sonich-Mullin et al. (2001) provided a framework for evaluating MOA of chemical carcinogenesis in animals and recognized the importance of moving on to the next step in the overall characterization of cancer hazard and risk in humans: the assessment of relevance of the MOA of animal carcinogenesis to humans. Adoption of the MOA framework concept is proceeding through its incorporation in the revised U.S. EPA Risk Assessment Guidelines for Carcinogens (U.S. EPA, 1999, 2005), and is now commonly used by other regulatory agencies and international organizations. In the United Kingdom (UK), the framework is being used for the assessment of pesticides and industrial chemicals. The UK Committee on Carcinogenicity has noted its value with regard to both harmonization between agencies and internal consistency in its latest Guidelines (COC, 2004). It has also been adopted and is being used by agencies in Australia and in Canada, in the evaluation of Existing Chemicals under the Canadian Environmental Protection Act. The European Union has incorporated the framework into the technical guidance documents that are being updated on evaluating new and existing industrial chemicals and biocides, including carcinogenicity. With regard to international organizations, of particular note is the use of the framework by the WHO/FAO Joint Meeting on Pesticide Residues (JMPR) in its evaluation of pyrethrin extract and its incorporation into the resulting monograph. *[Peer reviewers are invited to provide further examples].*

The step to extend this concept to human relevance is being taken forward by IPCS in cooperation with international partners. It was the subject of an IPCS international workshop convened in Bradford, United Kingdom, from 21-23 April 2005. This workshop prepared draft text for a unified IPCS Framework, including updating the 2001 Mode of Action Framework. The framework text, and the steps leading to its development are discussed in detail in the following sections.

## **THE 2001 IPCS CONCEPTUAL MOA FRAMEWORK FOR CANCER RISK ASSESSMENT**

### **Purpose of the Framework**

The IPCS Mode of Action Framework remains a fundamental basis for the unified IPCS Framework for Analysing the Relevance of a Cancer Mode of Action for Humans. The framework provides a generic approach to the principles commonly used when evaluating a postulated MOA for tumour induction in animals by a chemical carcinogen. Thus, the framework is a tool that provides a structured approach to the assessment of the overall weight of the evidence for the postulated MOA. It outlines the thought processes involved in making use of mechanistic data in risk assessment in a structured way. In this context, a supported MOA would have evidence provided by robust mechanistic data to establish a biologically plausible explanation.

The framework is designed to bring transparency to the analysis of a postulated MOA and, thereby, promote confidence in the conclusions reached through the use of a defined procedure which mandates clear and consistent documentation of the facts and reasoning including inconsistencies and uncertainties in the available data. The animal MOA framework analysis is the first step in the hazard characterization process and can be greatly aided by the presentation of tabular summaries of comparative data on incidence of intermediate endpoints and tumours. It is also envisaged that the framework will be useful to both regulators and researchers in identifying research needs based on clear delineation of data gaps and inconsistencies.

The animal MOA framework is not a checklist of criteria, but rather an analytical approach. The purpose of the framework is to provide a systematic means of considering the weight of the evidence for a MOA in a given situation; it is not designed to give an absolute answer on sufficiency of the information as this will vary depending on the circumstance. It is envisaged that the animal MOA framework will be helpful in performing risk assessments of chemical carcinogens across all sectors (drugs, industrial chemicals, pesticides, food additives, etc.). In the resulting risk assessment documentation, the framework analysis could be appropriately positioned within the hazard characterization section. It may be regarded as an essential precursor to any discussion of human relevance, dose-response relationships and risk characterization. The framework may also find use as a stand-alone analytical tool, and it is, therefore, important that the relevant studies on which the conclusions are based be fully referenced in the text of the framework analysis.

A mode of action, comprising the same set of key events, may apply to many different compounds. The evidence necessary to establish that a specific mode of action is responsible for a given carcinogenic response will be substantial the first time such a mode of action is proposed. As subsequent compounds are found to share this mode of action, the “barrier” to acceptance will become lower, though it will always be necessary to establish rigorously that the key events comprising the mode of action occur, and that they fulfil the criteria indicated below.

Expert judgment and peer review are essential elements for a given mode of action to be accepted as responsible for a carcinogenic response. Acceptance does not necessarily mean unanimity, but a majority of the scientists reviewing the MOA should agree that the relevant scientific information has been identified and appropriately analysed, that the “key events” have been identified and are supported by the information presented, that their relationship to carcinogenesis has been clearly established in the hypothesized MOA and that alternate MOAs have been considered and rejected. It is important to emphasize that review of a MOA concerns its key elements and does not need to be tissue-specific. Thus, a MOA that has previously been peer reviewed and accepted for one tissue and which is applicable to other tissues does not need to be subjected to the scientific review and acceptance process. For example, cytotoxicity and consequent regeneration is a well-known and well-documented mode of action for a wide variety of chemicals that affect different tissues.

Scientific peer participation is a prerequisite to acceptance of a postulated mode of action. Peer participation includes both peer involvement and peer review. Peer involvement implies that the hypothesized MOA is the product of the collective efforts of a number of scientists who have identified, reviewed and analysed data and formulated the MOA hypothesis. Peer review implies that the proposed MOA has been critically reviewed by scientists independent of the process of development of the MOA. In many cases, this peer review may include publication in the scientific literature, allowing for widespread review and comment. Presentations and discussion at scientific meetings and workshops also constitute peer involvement that contributes to acceptance by the scientific community.

As knowledge advances, the characterization of a MOA will change. Additional key events may be identified, and others may be refined or even dropped. Nevertheless, significant changes to the key events also need some general acceptance, through peer review, such as described above.

It is important that a compendium of agreed modes of action be constructed and maintained in a publicly accessible location. Ideally this should be a website. This would comprise a series of MOAs and their associated key events, for reference by those developing framework analyses for compounds which may act by similar modes of action.

To assist in the dissemination and application of the unified IPCS Framework a database of informative cases should be constructed and maintained. These would comprise worked examples that have been analysed using the framework, to provide an indication of the relevant level of detail of the analyses and nature of the weight of evidence required to support acceptance of a proposed MOA in causing the carcinogenic response. Such cases would be particularly valuable early in the development of a new MOA.

Some mechanism will need to be established to judge the stage of acceptability of proposed modes of action and modifications to existing modes of actions, perhaps through a series of international workshops.

## **Framework Guidelines: Proposed Section Headings**

In development of the unified IPCS Framework, the 2001 MOA Framework text has been updated and this revised version is presented below.

### ***1. Introduction***

This section describes the cancer endpoint or endpoints that have been observed and identifies which of these is addressed in the analysis. The nature of the framework is such that only one mode of action is analysed at a time; hence, for example, tumour types associated with a different mode of action, even if recorded in the same animals, will require separate framework analyses. However, where different tumours are induced by the same (or a very similar) mode of action, they are best addressed in a single analysis.

### ***2. Postulated mode of action (theory of the case)***

This section comprises a brief description of the sequence of events on the path to cancer for the postulated mode of action of the test substance. This explanation of the sequence of events leads into the next section which identifies the events considered “key” (*i.e.* necessary and measurable) given the data base available for the analysis.

### ***3. Key events***

This section briefly describes the “key events” — *i.e.* measurable events that are critical to the induction of tumours as hypothesized in the postulated mode of action. To support an association, a body of experiments needs to define and measure an event consistently. Pertinent observations, *e.g.* tumour response and key events in same cell type, sites of action logically relate to event(s), increased cell growth, specific biochemical events, changes in organ weight and/or, histology, proliferation, perturbations in hormones or other signalling systems, receptor-ligand changes, effects on DNA or chromosomes, and impact on cell cycles.. For example, key events for tumours hypothesized to be associated with prolonged regenerative proliferation might be cytotoxicity as measured histopathologically and an increase in labelling index. As another example, key events for induction of urinary bladder tumours hypothesized to be due to formation of bladder stones composed primarily of calcium phosphate might include elevated urinary calcium, phosphate and pH and formation of bladder stones followed by irritation and regenerative hyperplasia of the urothelium.

### ***4. Dose–response relationship***

This section should characterize the dose–effect/response relationships for each of the key events and for the tumour response, and discuss their inter-relationships, with particular reference to the shape of the dose-effect/response curves and to any thresholds. Ideally, one should be able to correlate the dose-dependency of the increases in incidence of a key event with increases in incidence or severity (*e.g.* lesion progression) of other

key events occurring later in the process, and with the ultimate tumour incidence. Comparative tabular presentation of incidence of key events and tumours is often helpful in examining dose–response.

The biological plausibility of any postulated mode of action in humans depends on a consideration of dose-effect and dose-response relationships. If a high experimental dose of a given compound is needed to result in an obligatory step in a mode of action, then the relevance to human risk becomes a matter of exposure. Thus, the exposure assessment step of the subsequent risk characterization is critical to the proper evaluation of human cancer potential.

It is important to consider whether there are fundamental differences in the biological response (i.e., dose transitions) at different parts of the dose response curve for tumour formation (Slikker et al, 2004). If so, key events relevant to the different parts of the dose-response curve will need to be defined and used in the framework analysis.

### ***5. Temporal association***

This section should characterize the temporal relationships for each of the key events and for the tumour response. The temporal sequence of key events leading to the tumour response should be determined. Key events should be apparent before tumour appearance and should be consistent temporally with each other; this is essential in deciding whether the data support the postulated mode of action. Observations of key events at the same time as the tumours (*e.g.* at the end of a bioassay) do not contribute to considerations of temporal association, but can contribute to analysis in the next section. Most often, complete data sets to address the criterion of temporality are not available.

### ***6. Strength, consistency and specificity of association of tumour response with key events***

This section should discuss the weight of evidence linking the key events, precursor lesions and the tumour response. Stop/recovery studies showing absence or reduction of subsequent events or tumour when a key event is blocked or diminished are particularly important tests of the association. Consistent observations in a number of such studies with differing experimental designs, increases that support since different designs may reduce unknown biases or confounding. Consistency, which addresses repeatability of key events in the postulated mode of action for cancer in different studies is distinguished from coherence, however, which addresses relation of the postulated mode of action with observations in the broader database (see point 7). Pertinent observations are, *e.g.*, tumour response and key events in same cell type, sites of action logically related to event(s), initiation–promotion studies, and stop/recovery studies.

### ***7. Biological plausibility and coherence***

The postulated mode of action and the events that are part of it need to be based on current understanding of the biology of cancer to be accepted, though the extent to which biological plausibility as a criterion against which weight of evidence is assessed is necessarily limited, due to considerable gaps in our knowledge in this regard. One should consider whether the mode of action is consistent with what is known about

carcinogenesis in general (biological plausibility) and in relation to what is also known for the substance specifically (coherence). For the latter, likeness of the case to that for structural analogues may be informative (*i.e.* structure–activity analysis). Information from other compounds that share the postulated MOA may be of value, such as sex, species and strain differences in sensitivity and their relationship to key events. Additionally, this section should consider whether the database on the agent is internally consistent in supporting the purported mode of action, including that for relevant non-cancer toxicities. Some modes of action can be anticipated to evoke effects other than cancer, *e.g.* reproductive effects of certain hormonal disturbances that are carcinogenic. Moreover, some modes of action are consistent with an observed lack of genotoxicity. Coherence, which addresses relation of the postulated mode of action with observations in the broader database — for example, association of mode of action for tumours with that for other endpoints — needs to be distinguished from consistency (addressed in Point 6 above) which addresses repeatability of key events in the postulated mode of action for cancer in different studies.

### **8. Other modes of action**

This section discusses alternative modes of action that logically present themselves in the case. If alternative modes of action are supported, they need their own framework analysis. These should be distinguished from additional components of a single mode of action which likely contribute to the observed effect, since these would be addressed in the analysis of the principal mode of action.

### **9. Uncertainties, Inconsistencies, and Data Gaps**

Uncertainties should include those related to both the biology of tumour development and those for the database on the compound of interest. Inconsistencies should be flagged and data gaps identified. For the identified data gaps, there should be some indication of whether they are critical as support for the postulated mode of action or simply serve to increase confidence therein.

### **10. Assessment of postulated mode of action**

This section should include a clear statement of the outcome with an indication of the level of confidence in the postulated mode of action — *e.g.* high, moderate or low. Consideration needs to be given as to whether any identified MOA is the same as that proposed for other compounds. If so, the extent to which the key events fit this MOA needs to be stated explicitly. Any major difference should be noted, and their implications for the MOA discussed. If a novel MOA is being proposed this should be clearly indicated.

## **ADDRESSING THE ISSUE OF HUMAN RELEVANCE**

In 2000, an IPCS Harmonization Project Cancer Planning Work Group<sup>2</sup> convened in Carshalton, United Kingdom (IPCS, 2000). Among the recommendations of that

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<sup>2</sup> This initial IPCS Working Group differed in membership from the subsequent IPCS working group convened to work on the human relevance project.

meeting was the suggestion that IPCS and ILSI move forward together and in parallel on the development of the extension of the IPCS MOA Framework toward addressing human relevance. It was recognized that ILSI could provide much help in technical workshops. In June 2001, the International Life Sciences Institute Risk Science Institute (ILSI/RSI) with support from the US EPA and Health Canada formed a working group to examine key issues in the use of mode of action information to determine the relevance of animal tumours. These efforts have resulted in several published reports that are described below. An IPCS Cancer Working Group, convened on 3-5 March 2004 in Arlington, Virginia, USA agreed that these reports should form the starting point for further exploration of the issue of human relevance of animal tumours by IPCS with the goal of developing a unified IPCS framework for use of MOA information in risk assessment for regulatory and other purposes (IPCS, 2004).

To address the issue of the human relevance of the MOA(s) determined in animals, ILSI/RSI charged its working group with expanding the IPCS MOA Framework to include evaluation of the human relevance of a cancer MOA determined in animals. The details of the process, the case studies, and the framework are published as a series of papers in the November 2003 issue of *Critical Reviews in Toxicology (CRTJ)* (Cohen et al., 2003; Meek et al., 2003). These articles briefly describe the ILSI/RSI Human Relevance Framework (HRF) and provide a user's guide for its application. In addition, references to specific examples on which the framework is based are included. Several iterations of case studies of chemicals with generally well-known modes of action were used to develop the integrated framework. The intent was to provide guidance for a disciplined, transparent process evaluating the mode of action in animals and each key event with respect to human relevance.

The ILSI/RSI HRF is based on three fundamental questions:

1. Is the weight of evidence sufficient to establish the mode of action (MOA) in animals?
2. Are key events in the animal MOA plausible in humans?
3. Taking into account kinetic and dynamic factors, are key events in the animal MOA plausible in humans?

These are followed by an explicit description of confidence in the evaluation, identification of specific data gaps, and the implications for risk assessment. It was emphasized by ILSI/RSI that use of this framework would form part of the hazard characterization step of the overall risk assessment process.

## **DEVELOPMENT OF A UNIFIED IPCS FRAMEWORK GUIDANCE DOCUMENT BASED ON THE IPCS MOA FRAMEWORK AND THE ILSI/RSI HRF**

The 2004 IPCS Cancer Working Group discussed the type of document that would be produced as a result of its task to extend the MOA Framework to address

human relevance. It was recognized that one integrated guidance document (a "unified framework") that worked as a whole would be needed to facilitate uptake and use by regulatory and other risk assessment bodies. The guidance could be supplemented by including publication of the other materials generated through the process (e.g. issues papers and case studies).

Overall, there was general agreement among Working Group members that the questions identified as the critical components of the ILSI/RSI HRF were important and appropriate for addressing the issue of human relevance of a mode of action determined in animals. However, several issues were identified that could benefit from additional clarification, development or expansion. These issues are addressed in the IPCS effort and result in modification of the ILSI/RSI HRF.

The unified IPCS Framework, developed by adopting the ILSI/RSI HRF and by modifying it as discussed by the Cancer Working Group and at a Workshop convened for this purpose in Bradford, UK, 21-23 April, 2005 (IPCS, 2005), is presented as an approach to answering a series of three questions, leading to a documented, logical conclusion regarding the human relevance of the MOA underlying animal tumours. The application of the guidance results in a narrative with four sections that may be incorporated into the hazard characterization of a risk assessment. The sections are as follows (see Figure 1.):

1. Is the weight of evidence sufficient to establish a mode of action (MOA) in animals?
2. Can human relevance of the MOA be reasonably excluded on the basis of fundamental, qualitative differences in key events between experimental animals and humans?
3. Can human relevance of the MOA be reasonably excluded on the basis of quantitative differences in either kinetic or dynamic factors between experimental animals and humans?
4. Conclusion: Statement of confidence, analysis, and implications.

In applying this framework for a given chemical, tumours of each animal target organ observed are evaluated independently, with the assumption that different modes of action are possible in different organs, though based on this analysis, modes of action in different tissues may be similar. Similarly, an evaluation of the likelihood of congruence between target organ(s) in different species and in humans needs to be made, based on the mode of action analysis.

### **Is the Weight of Evidence Sufficient to Establish a Mode of Action in Animals?**

Answering this first question in the unified IPCS Framework requires application of the (updated) IPCS MOA Framework described earlier in this document. The steps in the MOA Framework are:

- A. Postulated MOA.

- B. Key Events; associated critical parameters.
- C. Dose Response Relationships.
- D. Temporal Association.
- E. Strength, Consistency and Specificity of Association of Key Events and Tumour Response.
- F. Biological Plausibility and Coherence.
- G. Possible Alternative MOAs.
- H. Uncertainties, Inconsistencies, and Data Gaps.
- I. Conclusion about the MOA.

This process incorporates an evaluation of the weight of evidence for possible alternative MOAs at a given **site**, and an evaluation of the overall strength of evidence supporting the MOA under consideration. Ultimately, a decision concerning the weight of evidence supporting the MOA and the level of confidence in that decision must be made. It also identifies critically important data gaps which, when filled, would increase confidence in potential modes of action. It is also necessary to establish whether the postulated MOA has already been described for other chemicals, in which case there will be information available on human relevance, or whether the proposed MOA is novel, in which case human relevance needs to be assessed *de novo*.

For a given chemical, the primary sources of information for evaluating a MOA are often likely data generated for that specific chemical in the animal model in which tumours were produced. Obviously, data from other sources can and should also be used, as appropriate, along with data on chemicals with similar chemical structures, the same or similar modes of action, or both. If the mode of action for a chemical is novel, considerably more data will be required to support the conclusion that it is related to the carcinogenic process of the tumours induced by that chemical than subsequent examples of chemicals acting by the same mode of action. The ILSI/RSI working group and the IPCS Bradford Workshop did not address the issue of how much data is sufficient to support a specific mode of action for a given chemical, except by way of example within the case studies and recognition that acceptance of a MOA requires scientific consensus (see above). Consideration at this stage of the mode of action in the context of potential variations between animals and humans also facilitates addressing subsequent steps in the framework.

**Can human relevance of the MOA be reasonably excluded on the basis of fundamental, qualitative differences in key events between experimental animals and humans?**

The wording of this question was changed from that in the ILSI/RSI HRF, following discussion at the IPCS Workshop on the implications of a Yes or a No answer to the original question. In answering the original question, only an unequivocal No would be sufficient to permit the conclusion that the animal MOA was not relevant to humans. Also, it was recognized that translation of the word "plausible" into other languages could be problematic. The question was therefore reworded to enable a Yes/No answer, but qualified by the descriptor "reasonably", based on recognition that

decisions about the adequacy of weight of evidence are not absolute but involve judgment based on transparent analysis.

This step represents a qualitative assessment of the relevance of the MOA to human cancer potential. Listing the critical specific key events that occur in the animal mode of action and directly evaluating whether each of the key events might or might not occur in humans facilitates consideration and transparent presentation of the relevant information. Presentation in tabular form, referred to as a concordance table, can be helpful in delineating the relevant information. (for an example see Meek et al, 2003; Case Study 6: kidney and liver tumours associated with chloroform exposure, Table 7, p. 630) The key events (and possibly some of the critical associated processes) are listed with the information regarding these events for the animals in which the tumour was observed. It is intended that the information in these tables be brief, since a narrative explanation is expected to accompany the table. In the right-hand column, the effect on humans for each of the key events is evaluated. An additional column for the results in a different strain, species, sex, or route of administration that does not result in tumours can be useful if information is available for comparison to the model that leads to tumours. In addition, factors may be identified that, whilst not key themselves, can modulate key events and so contribute to differences between species. Such factors include genetic differences in pathways of metabolism, competing pathways of metabolism, cell proliferation induced by concurrent pathology. Any such factors identified should be noted in a footnote to the concordance table.

The evaluation of the concordance for a given chemical in humans is an evaluation of the MOA in humans, rather than an evaluation of the specific chemical. In general, the initial key events are likely more chemical-specific, for example the induction response by phenobarbital in rodent liver, or the formation of a cytotoxic metabolite from chloroform by CYP2E1. Later events would be more generic to the MOA, for example pleiotropic stimulation of hepatic proliferation or regenerative hyperplasia. Information that can be utilized to evaluate the key events in humans can come from *in vitro* and *in vivo* studies on the substance itself, but also can involve basic information regarding anatomy, physiology, genetic disorders, epidemiology, and any other information that is known regarding the key events in humans. Information concerning an evaluation of the key event in humans exposed directly to the specific chemical is almost always unavailable.

In evaluating the concordance of the information in humans to that in animals, a narrative describing the weight of evidence and an evaluation of the level of confidence for the human information needs to be provided. Some specific types of information that are useful include the following:

1. Cancer incidences at the anatomical site and cell type of interest, including age, sex, ethnic differences and risk factors, including chemicals and other environmental agents.

2. Knowledge of the nature and function of the target site including development, structure (gross and histologic), and control mechanisms at the physiological, cellular, and biochemical levels.
3. Human and animal disease states that provide insight concerning target organ regulation and responsiveness.
4. Human and animal responses to the chemical under review or analogs following short, intermediate, or long-term exposure, including target organs and effects.

Obviously, a substantial amount of information is required to conclude that the given mode of action is not relevant to humans. If such a conclusion is strongly supported by the data, then chemicals producing animal tumours only by that mode of action would not pose a cancer hazard to humans and no additional risk characterization for this endpoint is required. Since there is no cancer hazard, there is no cancer risk for the tumour under consideration.

The question of relevance considers all groups and life-stages. It is possible that the conditions under which a mode of action operates occur primarily in a susceptible sub-population or life-stage, for example, in those with a pre-existing viral infection, hormonal imbalance, or disease state. Special attention is paid to whether tumours could arise from early-life exposure, considering various kinetic and dynamic aspects of development during these life-stages. Any information suggesting quantitative differences in susceptibility is identified for use in risk characterization.

**Can human relevance of the MOA be reasonably excluded on the basis of quantitative differences in either kinetic or dynamic factors between experimental animals and humans?**

The wording of this question was changed from that in the ILSI/RSI HRF, following discussion at the IPCS Workshop on the implications of a Yes or a No answer to the original question. In answering the original question, only an unequivocal No would be sufficient to permit the conclusion that the animal MOA was not relevant to humans. The question was therefore reworded to enable a Yes/No answer, but qualified by the descriptor “reasonably”, based on recognition that decisions about the adequacy of weight of evidence are not absolute but involve judgment based on transparent analysis.

For purposes of human relevance analysis, if the experimental animal MOA is judged to be qualitatively relevant to humans, a more quantitative assessment is required that takes into account any kinetic and dynamic information that is available from both the experimental animals and humans. Such data will of necessity be both chemical and MOA specific and will include the biologically effective doses required to produce the relevant kinetic and dynamic responses from which neoplasia can arise. Kinetic considerations include the nature and time course of chemical uptake, distribution, metabolism and excretion, while dynamic considerations include the consequences of the interaction of the chemical with cells, tissues and organs. On occasion, the biologically

effective dose that would be required to create these conditions would not be possible in humans. It may also be that quantitative differences in a biological process involved in a key event, for example the clearance of a hormone, are so great that the animal MOA is not relevant to humans. However, the IPCS Workshop recognised that only in rare instances is it likely that it will be possible to dismiss human relevance on the basis of quantitative differences. As with the qualitative assessment, a tabular comparison of quantitative data from the experimental animals and humans can facilitate the evaluation (for example, see Meek et al, 2003; Case study 5, thyroid tumors associated with exposure to Phenobarbital, Table 6, p. 624). Useful comparisons can also be made with key events identified from studies of other compounds believed to induce effects by a similar MOA.

### **Statement of Confidence, Analysis, and Implications**

Following the overall assessment of each of the three questions, a statement of confidence is necessary that addresses the quality and quantity of data underlying the analysis, consistency of the analysis within the framework, consistency of the database, and the nature and extent of the concordance analysis. An evaluation of alternative modes of action, using comparable analyses and rigor, is also essential. A critically important outcome of adequate consideration of the weight of the evidence for an overall mode of action and the qualitative and quantitative concordance is the identification of specific data gaps that can be addressed experimentally in future investigations to increase confidence.

In rare circumstances, there may be conclusive epidemiological data on the cancer risk from a chemical that shares the MOA of the compound under consideration, i.e. the compound does or does not cause cancer in humans. Obviously, such data would lend considerable weight to the conclusion of the human relevance evaluation. However, there may be occasions when, despite it being possible to establish an MOA in animals, there is insufficient information on the key events in humans to reach a clear conclusion on human relevance. In such circumstances it might be possible to bridge this data gap by using epidemiological data. For example, the database on key events in humans for compounds that act like phenobarbital to induce hepatic tumours is incomplete. However, there are robust epidemiological data showing that exposure to phenobarbital for prolonged periods at relatively high doses does not cause cancer in humans. One possibility therefore, is to “read across” from these findings with phenobarbital to any other compound that shares its MOA in animals in inducing rodent liver tumours and to conclude that the tumours caused by such a compound are not relevant to the risk assessment of the compound in humans. Such a conclusion would be critically dependent on the reliability of the epidemiological data and the similarity between the MOA for the chemical under test to that of the compound for which there are epidemiological data available.

In applying the framework to case studies, it is apparent that much current research does not address key questions that would facilitate an analysis of an animal MOA or its relevance to humans. Often this has been because of lack of transparent

delineation of key data gaps based on consideration of the data in analytical frameworks such as that presented here.

Also, the output of formal human relevance analysis is not restricted to determination of whether or not an endpoint in animals is relevant to humans. Rather, consideration of the relevant information in a transparent, analytical framework provides much additional information which is critically important in subsequent steps in the risk characterization for relevant effects. Based on a human relevance analysis for a proposed mode of action for relevant effects, it may be possible to predict, for example, site concordance or not of observed tumours in animals to humans. Analysis often also provides indication of those components of a proposed mode of action which may only operate over a certain dose range. This needs to be noted and addressed subsequently in risk characterization. It also often provides information on relevant modulating factors which are likely to affect risk.

Importantly, it also contributes to identification of any special sub-populations (e.g., those with genetic predisposition) who are at increased risk and often provides information relevant to consideration of relative risk at various life stages. In some cases, this may not be based on chemical-specific information but rather inference, based on knowledge of the mode of action as to whether or not specific age groups may be at increased or decreased risk.

The data and their analysis using the framework should be reported in a transparent manner, enabling others to determine the basis of the conclusions reached with respect to the key events, the exclusion of other MOAs and the analysis of human relevance. As the specific form of presentation will vary with the type of data available, it is not helpful to be prescriptive on how the information should be reported. However, presentation should include sufficient details on the context and thought processes to ensure transparency of the conclusions reached. The use of appropriate tables can be helpful in presenting certain data such as comparative analysis of key events in experimental animals and humans.

### **Application of the IPCS Framework to DNA-reactive carcinogens**

Because of similarities in the carcinogenic process between rodents and humans and the comparable initial interactions with DNA by DNA-reactive carcinogens, it would be expected that, in general, DNA-reactive carcinogens would be assessed as progressing to the step of "YES, the key events in the animal MOA could occur in humans" in the ILSI/RSI HRF as was the case for ethylene oxide (Meek et al., 2003) and "NO", to the equivalent step in the IPCS Framework which asks the question "can human relevance of the MOA be reasonably excluded on the basis of fundamental qualitative differences in key events between animals and humans". In a recent paper, Preston and Williams (2005, in press) presented a set of key events for tumour development that provided a guide for the use of the ILSI/RSI HRF with DNA-reactive carcinogens. This guide supported the view that for most DNA-reactive chemicals, the animal MOA would be predicted to occur in humans. However, it was also argued that there could be exceptions and that the

ILSI/RSI HRF would be a valuable tool for identifying these. The ILSI/RSI HRF and the IPCS Framework can also assist in quantifying differences in key events between rodents and humans that may be of value in extrapolating risk to humans. Not all rodent DNA-reactive carcinogens have been established to be human carcinogens as judged by the IARC review process. For some of these exceptions, this human-rodent difference in tumour response is attributable to lower exposure of humans to the agent or to the relative insensitivity of epidemiological studies to detect tumour responses at low exposure levels. However, there are other reasons for such differences that are based on biological considerations. For example, if a DNA-reactive carcinogen induces tumours *only* in a species-specific organ (e.g., Zymbal gland in rodents), it is possible that the animal MOA based on key events might not occur in humans, though available data on mode of action would need to be considered to permit such a conclusion.. Similarly, the generally more proficient DNA repair processes that occur in humans than in rodents or a unique pathway of bioactivation in rodents could result in there being “YES” answers to the steps in the IPCS Framework that address the queries “ Can human relevance of the MOA be reasonably excluded on the basis of fundamental qualitative differences in key events between animals and humans ?” and/or “Can human relevance of the MOA be reasonably excluded on the basis of quantitative differences in either kinetic or dynamic factors between animals and humans?”. Alternatively, the IPCS Framework could provide quantitative information on these processes for use later in the risk characterization step.

The need in order to apply the IPCS Framework for DNA-reactive carcinogens is to develop a set of key events that would clearly describe the cancer process and use these as the guide for establishing the human relevance of a rodent tumour MOA for any particular DNA-reactive carcinogen under consideration

## CONCLUSIONS

As additional data relevant to identification of potential MOAs are obtained, it is becoming increasingly clear that there often are biological linkages among different types of toxic effects. In some cases, a MOA will lead to organ toxicity that in turn is a key event in the carcinogenic pathway for that organ. In other cases, a MOA may lead to toxic effects in multiple organs. In still other cases, a MOA may lead to different toxic effects at different life stages. Where appropriate the weight of evidence for an hypothesized MOA for these effects should be analysed in a consistent fashion. Application of the Framework would be an invaluable tool for harmonization across endpoints.

1. A unified IPCS Framework, based on the work by IPCS on a MOA framework and by ILSI RSI on a human cancer relevance framework has been developed.
2. Many aspects of the original frameworks have been adopted but a number of changes have been made to improve clarity and to introduce some elements not

- previously considered (e.g. sensitive sub-populations), based on experience gained in their application from the time since their publication.
3. The utility of the framework as an analytical tool within the overall risk assessment paradigm, i.e. in hazard characterization has been emphasized, and the role of exposure assessment in risk characterization has been clarified.
  4. Prior to embarking on a framework analysis, there needs to be careful evaluation of the weight of evidence for a carcinogenic response in experimental animals.
  5. Attention is drawn specifically to the need to consider potentially susceptible sub-groups, for example in different life stages or those with certain disease states.
  6. The importance of considering dose-effect and changes in effect at different parts of the dose-response curve leading to different key events for the MOAs at different doses has been emphasized.
  7. The need to separate key events from modulating factors and to consider their potential quantitative impact in the risk characterization was emphasized.
  8. The framework is applicable to all carcinogens, whatever the MOA. Some guidance is provided on developing MOAs for compounds that are DNA reactive.
  9. The process whereby a MOA is accepted is described.
  10. It is recommended that a compendium of MOAs with agreed key events be established and maintained.
  11. It is recommended that a database of cases where the framework has been utilized, particularly when early in the development of a MOA, should be compiled and maintained.
  12. It is concluded that the framework is of value to both risk assessment and research communities in identifying data needs in establishing a MOA.
  13. It is concluded that a qualitative scheme for the evaluation of mutagenic potential is of considerable value in the application of the framework and that updating of the IPCS scheme is recommended.
  14. It should be possible to extend the framework to non-cancer endpoints and further work on this is recommended.

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FIGURE 1. IPCS general scheme illustrating the main steps in evaluating the human relevance of an animal MOA for tumour formation. The questions have been designed to enable an unequivocal answer YES or NO, but recognizing the need for judgment regarding sufficiency of weight of evidence. Answers leading to the left side of the diagram indicate that the weight of evidence is such that the MOA is not considered relevant to humans. Answers leading to the right side of the diagram indicate either that the weight of evidence is such that the MOA is likely to be relevant to humans or that it is not possible to reach a conclusion regarding likely relevance to humans, due to uncertainties in the available information. In these cases, the assessment would proceed to risk characterization. It should be noted that only at this stage would human exposure be included in the evaluation.

